Constipation: Update on Evaluation and Management

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Defining Constipation: A Moving Target

• What do patients say?
  – Frequency – “go once or twice a week”
  – Stool Consistency – “hard” “lumpy”
  – Experience prior to or during BM – “bloated”, “abdominal pain”, “straining”, “urge but can’t go”

• What do GI societies say?
  – ROME IV / AGA / ACG
    • Chronic idiopathic / functional constipation (CIC/FC)
    • Irritable bowel syndrome with constipation predominance (IBS-C)
    • Opiate-induced constipation (OIC)
IBS-C vs. CIC / FC

ROME IV– IBS
Recurrent *abdominal pain* at least 1 day/week in the past 3 months associated 2 or more of the following:
   a) Related to defecation
   b) Associated with a change in stool frequency *
   c) Associated with a change in stool form *
*IBS-C sub-type requires predominant symptom meets CIC/ FC

ROME IV– CIC / FC
Two or more of the following (at least 25% of defecations):
   a) Straining
   b) Lumpy or hard stools
   c) Sensation of incomplete evacuation
   d) Sensation of anorectal obstruction / blockage
   e) Manual maneuvers to facilitate (e.g. splinting, digital evacuation)
   f) Fewer than 3 defecations per week
New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include CIC / FC criteria.
IBS-C and CIC: Truly Different Disorders?


Rey et al. (2014) Am J Gastroenterol 109:876–884

1) CIC and IBS-C have a significant overlap of symptoms

2) CIC and IBS exist on a continuum, and thus similar medications should be helpful
Constipation: A Major Impact

• Prevalence
  – IBS-C: ~4% of adults
  – CIC/FC: ~15% of adults; 33% in adults aged 60+
  – OIC: ~40% of non-cancer chronic opiate users

• Rising Costs:
  – Constipation related ED care in US $0.7B (2006) -> $1.6B (2011)
  – Newer drugs are more expensive

Chronic constipation is largely a problem seen in the outpatient setting.

Diagnostic evaluations constitute the biggest factor on the expense site.
INITIAL WORKUP

• History and Physical (rectal)
• Evaluate for common metabolic contributors
• Drug Review!
• Consider pelvic floor dyssynergia

• “Alarm symptoms”: sudden change in bowel habits after the age of 50 years, blood in stools, anemia, weight loss, and a family history of colon cancer.
INITIAL TREATMENT

1. Interview and physical examination
2. Consider metabolic and structural evaluation, baseline labs
3. Therapeutic trial – fiber ± laxatives
4. Inadequate response
   - Anorectal manometry balloon expulsion test*
     - Normal
       - Colonic transit
         - Slow
           - Slow transit constipation
         - Normal
           - Normal transit constipation
     - Inconclusive
       - Barium or MR defecography
       - Normal
         - Defecatory disorder
       - Abnormal
         - Abnormal

*Note: Anorectal manometry balloon expulsion test can be repeated if needed.
INITIAL TREATMENT

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Meds associated with Constipation

• Anticholinergics
• 5-HT3 antagonists (ondansetron)
• CCBs/BBs / diuretics
• Cation-containing agents (Iron/ Bismuth/ Calcium/ Lithium)
• Antipsychotics (Haldol, etc.)
• Dopamine agonists
• Sympathomimetics (ephedrines)
Common Medical Conditions Associated with Constipation

• **Metabolic**
  – DM, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, heavy metal poisoning

• **Myopathies**
  – Scleroderma; amyloidosis

• **Neuropathies**
  – Parkinson’s disease, spinal injury, CVA, MS

• **“Other”**
  – Depression, Autonomic neuropathy, Cognitive impairment, Immobility
Colonoscopy: Money Worth Spending?

Truly relevant findings are less common than in screening colonoscopies.

Colorectal Disease 14(5): 585-591
Endoscopy 42: 208-212
American Journal of Gastroenterology 105(4): 859-865
Only 1 of 873 patients with TSH testing had constipation as the only symptom of hypothyroidism.
Dyssynergic Defecation

• Present in ~33% of chronic constipation
• Anorectal manometry / BET

• Treatable with pelvic floor biofeedback (80%+ effective!)
Did we fix it? Moving Endpoints in Constipation Trials

• What does the FDA say?
  – ‘Adequate relief’ – binary (yes/no) → Likert scale
  – Subjective Global Assessment of Relief (1-10 / Likert scale)
  – BM frequency + Global Symptom Severity combined end-point
  – Complete spontaneous BM frequency + Global Symptom Severity combined end-point
Fixing Constipation Fixes Pain... No matter what you use

Fiber – the evidence

- Meta-analysis: **benefit**
- Psyllium, single or multi-fiber, >15 g
- Dose limiting side effects: bloating, flatulence

Overall
Type of fibre
Psyllium
Inulin
GOS
Mixture of inulin with RM
Prebiotics vs. non-prebiotics
Prebiotics
Prebiotics with non-prebiotics
Non-prebiotics
Single vs. multiple fibre
Single fibre
Multiple fibre
Dose of treatment
Low dose (≤15 g)
High dose (>15 g)

Favours control
Favours fibre
Standardized mean difference (95% CI)
Oral Medications for Constipation

• Target motility and/or secretion

• 4 FDA-approved drugs (3 available)
  – **Tegaserod**; FDA approved 2002 (IBS-C), 2004 (CIC); pulled in 2007
  – **Lubiprostone**; FDA approved 2008 (IBS-C and CIC)
  – **Linaclotide**; FDA approved 2012 (IBS-C and CIC)
  – **Naloxigol**; FDA approved 2014 (OIC)
Systemic Drugs for Constipation: Evaluating the Evidence

- Systemic therapies that have been evaluated for constipation (IBS-C, CIC, OIC):
  1) Are based on larger clinical trials (n>500)
  2) Show statistically significant, but only marginal benefits compared to placebo
  3) May have similar effect sizes to smaller trials using PEG-3350

- **Very expensive** and heavily marketed drugs
  - Competing interests; large market; large population
Lubiprostone

- Lubiprostone: Type 2 chloride channel (ClC-2) activator; promotes chloride-rich intestinal fluid secretion (small bowel)
  - In preclinical human studies, increased small intestinal and colonic motility
  - Likely to be useful for IBS-C and CIC
Lubiprostone: Clinical Trials

- IBS-C: Drossman et al. (2009)
  - Two double-blind, placebo-controlled RCTs using 8 mcg BID for 12 weeks
  - Total 1171 patients meeting Rome II IBS-C criteria
  - Primary end-point “overall responder”: Satisfactory relief of IBS symptoms (at least “moderately or significantly relieved”) at least 8 weeks of the study
  - Secondary end-points: pain/discomfort relief, among others.
LOCF = last observation carried forward

NNT = 12.8

Weekly responder rate

PAIN RESPONSES (unclear how quantified; 0-4 scale?)

Treatment = -0.43 (p=0.039)
Placebo = -0.35
Lubiprostone: Clinical Trials

• CIC: Johanson et al. (2008)
• Double-blind, placebo-controlled RCT using 24 mcg BID for 4 weeks
  – 242 patients; <3 SBMs/wk plus one additional symptom (straining, incomplete evacuation, hard and/or lumpy stools) >25% of the time
  – Primary end-point: frequent of SBMs in 1 week
  – Secondary end-points: pain/discomfort relief, among others.
Large Placebo Response

“Full Response” = at least 3 BMs/wk

NNT = 3.3

Johanson et al. (2008)
Linaclotide

- Linaclotide: guanylate cyclase-C (GC-C agonist)
  - Minimally absorbed, therefore acts on luminal surface / intestinal epithelial cells
- GC-C agonism -> cGMP release
  - Activation of signal transducers activates CFTR and increased luminal secretion
  - cGMP is also released extra-cellularly, and presumptively influences pain by reducing primary afferent firing rates
  - In preclinical human studies, increases small intestinal and colonic motility
  - Likely to be useful for IBS-C/CIC

Linaclotide: Clinical Trials

• IBS-C: Johnston et al. (2010)
• Double-blind, placebo-controlled RCT using up to 600 ug. for 12 weeks
  – 420 patients; more stringent criteria: Rome II IBS-C criteria AND “CIC” study-type criteria (<3 CSBM/s/wk plus one additional symptom (straining, incomplete evacuation, hard and/or lumpy stools) >25% of the time)
  – Primary end-point: # weekly CSBM; “75% responder” = ≥3 CSBM and an increase ≥1 above baseline for 75% of the treatment weeks
Primary End-Point (CSBM 75% responder)
Placebo -- 11.8%
300 ug Linaclotide – 32.1%  \(\text{(NNT} = 4.9)\)
600 ug Linaclotide – 23.6%  \(\text{(NNT} = 8.5)\)

Johnston et al. (2010)
Linaclotide: Clinical Trials

- CIC: Lembo et al. (2011)
- Two double-blind, placebo-controlled RCTs using 145 or 290 ug daily for 12 weeks
  - 1276 patients; standard “CIC” study-type criteria
    (<3 CSBMs/wk plus one additional symptom (straining, incomplete evacuation, hard and/or lumpy stools) >25% of the time)
  - Primary end-point: “75% responder” -> ≥3 CSBMs and an increase ≥1 above baseline for 75% of the treatment weeks
  - Secondary end-points: pain, bloating, etc.
Abdominal Pain Relief
(Decrease of ≥0.5 pts in 75% Of the study weeks)

Placebo                   – 21.1%
145 ug Linaclotide – 33.6%  NNT = 8
290 ug Linaclotide – 31.9%  NNT = 10.8

Lembo et al. (2011)
Naloxegol

- Peripherally acting, orally available mu-opiate receptor antagonist
- Would be expected to reduce opiate-induced constipation
- Prior studies showed methylnatrexone (IV/SQ medication) to be effective
Naloxegol

- Chey et al (2014) – NEJM
- Two identical phase 3, double-blind studies (652 and 700 pts)
  - Noncancer pain and opioid-induced constipation
  - Randomized to daily dose of 12.5 or 25 mg of naloxegol or placebo
  - The primary end point was the 12-week response rate (≥3 spontaneous bowel movements per week and an increase from baseline of ≥1 spontaneous bowel movements for ≥9 of 12 weeks and for ≥3 of the final 4 weeks) in the intention-to-treat population.
  - Secondary end points were the response rate in the subpopulation of patients with an inadequate response to laxatives before enrollment, time to first post dose spontaneous bowel movement, and mean number of days per week with one or more spontaneous bowel movements

Naloxegol

A Response Rates in the ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Study 04</th>
<th>Study 05</th>
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<tbody>
<tr>
<td>Naloxegol, 12.5 mg</td>
<td>40.8</td>
<td>34.9</td>
</tr>
<tr>
<td>Naloxegol, 25 mg</td>
<td>44.4</td>
<td>39.7</td>
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<tr>
<td>Placebo</td>
<td>29.4</td>
<td>29.3</td>
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<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>Study 04</th>
<th>Study 05</th>
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<tbody>
<tr>
<td>1.38 (1.06–1.80)</td>
<td>1.51 (1.17–1.95)</td>
<td>1.19 (0.91–1.55)</td>
</tr>
<tr>
<td>1.51 (1.17–1.95)</td>
<td>1.35 (1.05–1.74)</td>
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<table>
<thead>
<tr>
<th>P Value</th>
<th>Study 04</th>
<th>Study 05</th>
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<tr>
<td>0.02</td>
<td>0.001</td>
<td>0.20</td>
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<table>
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<tr>
<th>No. Needed to Treat</th>
<th>Study 04</th>
<th>Study 05</th>
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<tr>
<td>8.8</td>
<td>6.7</td>
<td>17.8</td>
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<tr>
<td>9.7</td>
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Coming down the pipeline: Elobixibat

- Ileal bile acid reabsorption inhibition
  - Target group is CIC

Chey WD et al. (2011) Am J Gastro 106:1803-1812

Coming down the pipeline for OIC

- Orally available methylnaltrexone
  - FDA approved July 22, 2016
Oral Medications for Constipation (Off-Label)

• Cholinergics
  – Bethanechol, pyridostigmine

• Colchicine (0.6 mg PO TID)

• Misoprostol (200-600 mcg PO daily)
Are any of these drugs better than PEG-3350?

• IBS-C: Chapman et al. (2013)
• Double-blind, placebo-controlled RCT using one to three doses of PEG-3350 for 4 weeks
  – 139 patients; Rome III criteria for IBS-C
  – Primary end-point: Number of SBMs per day during Week 4
  – Secondary end-points: CSBMs/wk, pain, bloating, etc.
Chapman et al. (2013)

Table 2. Efficacy analysis

<table>
<thead>
<tr>
<th>Variable (weekly mean±s.d.)</th>
<th>PEG 3350+E</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>Between-group difference at week 4 (95% CI), P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-In</td>
<td>Week 4</td>
<td>Run-In</td>
<td>Week 4</td>
<td></td>
</tr>
<tr>
<td>SBM number&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.28±0.91</td>
<td>4.40±2.58</td>
<td>1.37±0.85</td>
<td>3.11±1.94</td>
<td>1.56 (1.17, 1.95), P&lt;0.0001</td>
</tr>
<tr>
<td>Severity of abdominal discomfort/pain&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1.57±0.91</td>
<td>1.23±0.95</td>
<td>1.53±0.98</td>
<td>1.23±0.88</td>
<td>-0.04 (-0.16, 0.08), P&gt;0.05</td>
</tr>
<tr>
<td>SCBM number&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.56±0.76</td>
<td>2.51±2.72</td>
<td>0.56±0.73</td>
<td>1.74±1.87</td>
<td>0.77 (0.42, 1.12), P&lt;0.0001</td>
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PEG-3350 (Miralax): Clinical trials

- CIC: DiPalma et al. (2007)
- Double-blind, placebo-controlled RCT using single daily 17g dose of PEG-3350 for 6 months
  - 304 patients; typical CIC criteria
  - Primary end-point: 50% or better in the number of weeks with greater than 3 CSBM

**RESULTS:**

- PLACEBO – 11%
- PEG-3350 – 52% \( (\text{NNT} = 2.4) \)
New meds vs. PEG for IBS-C, CIC, or OIC?

• Large clinical trials have shown statistically significant, but marginal effects for tegaserod, lubiprostone, linaclotide, and naloxagol
  – NNT analysis: most end-points with NNT > 3 (and up to 10-12)

• Small clinical trials using modest doses of PEG-3350 have shown some efficacy, in a range not dissimilar to the systemic medication trials
  – NNT analysis: 2.4 for CIC
Time To Quit?

Subtotal Colectomy for Constipation

How often is it done?
How well does it work?
Time Trends

• About 15% of colectomies performed in the US after for chronic constipation
• Numbers are increasing

The American Surgeon 77(12): 1613-1618.
Outcomes

• Complication rates (30 days): ~30%.
• Small bowel obstruction within 1-5 years: 30%
• Reoperations within 1 year: ~10%
• Ileostomy rates within 5 years: ~10%

• Satisfaction: 50-90% (short term)
• Negative predictors: pain and comorbid psychiatric problems.
Summary: Chronic Constipation

• ...is common, but in many cases improves

• ...rarely requires extensive testing

• ...is treated increasingly with expensive prescriptions without convincing evidence of outcomes much better than OTC laxatives

• ...should VERY rarely lead to surgery.
Thanks!

• Questions?